

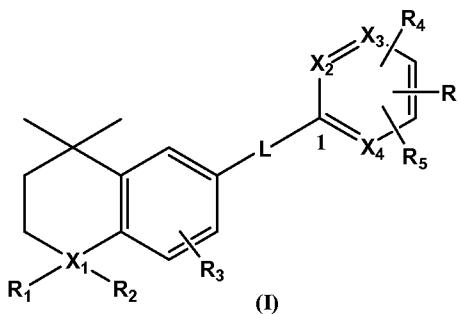
LEBLOND et al.
Appl. No. 10/581,947
Atty. Ref.: 3665-181
Supplemental Amendment
February 1, 2010

AMENDMENTS TO THE CLAIMS:

Please amend the claims as follows:

Claims 1-21. (Cancelled)

22. (Currently Amended) A compound having a general formula (I):



wherein:

R is $-C(O)NR_7R_8$, $-(CXY)_tC(O)NR_7R_8$, $-C(O)C(O)NHMe$, $-(C=C)C(O)NR_8R_9$, or $-C(O)CF_3$, or another Zn chelating group, with the proviso that R is not an acidic group or an ester derivative, COOR₉ or salt thereof, R₇ is a group of formula $-OH$, $-OR_9$, 2-aminophenyl and R₈ is selected from hydrogen, C₁₋₆alkyl; R₉ is independently selected from hydrogen or C₁₋₆alkyl ; t is 1, 2 or 3 (preferably 1), X and Y, which are identical or different, represent an hydrogen or halogen atom (preferably F),

X₁ represents a carbon, oxygen, nitrogen or sulphur atom,

R₁ and R₂ represent independently or form together:

[[.]]) a C₁₋₆alkyl group, in particular methyl or ethyl groups, when X₁ is a carbon atom,

[[.]]) nothing, when X₁ is a oxygen or sulphur atom,

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[[.]] one or two oxygen atoms, when X_1 is sulphur atom (the case of a sulfoxide – SO_- or a sulphone $-\text{SO}_2-$), or

[[.]] one atom of hydrogen, an alkyl, aryl or aralkyl group, when X_1 is an atom of nitrogen (the case of an amino $-\text{NH}$, -an N-alkyl, N-aryl or N-aralkyl group);

X_2 and X_3 , which are identical or different, represent CH, an atom of oxygen or an atom of nitrogen, or $X_2=X_3$ may be a single atom of sulphur, oxygen or nitrogen, or in the case where X_2 is an atom of oxygen and X_3 an atom of nitrogen, C_1 and X_4 represent a single one and same carbon atom, so that the ring carrying X_2 and X_3 can be an isoxazole ring,

X_4 can be CH or a nitrogen atom,

R_4 and R_5 , which are identical or different, represent a hydrogen atom, a halogen atom, ~~more particularly a fluorine atom~~, a C_{1-6} alkyl group, a group of formula $-\text{OH}$, $-\text{NH}_2$, $-\text{NHR}_6$, $-\text{OR}_6$, $-\text{SR}_6$, $-(\text{CF}_2)_n\text{CF}_3$, where n is an integer from 0 to 10, and whenever possible their salts with physiologically tolerated acids,

R_6 represents a hydrogen atom, a C_{1-6} alkyl group, a fluoroalkyl group having from 1 to 6 carbons atoms and from 3 to 7 fluorine atoms, an aryl group or an aralkyl group;

R_3 has the same definition as R_4 and R_5 ;

L is a linker and represents a bivalent radical either linear or cyclic, either saturated or unsaturated, more particularly L represents a bivalent radical derived from an alkane, alkene, alkyne or, aromatic or not, cyclic containing hydrocarbon group having from 1 to 12 carbon atoms, another bivalent radical of the following formula $-\text{O}-$,

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-CO-, -CO-NH-, -NH-CO-, -NH-CO-NH-, -CF₂-CO-NH-, -C(XY)-CO-NH-CH₂-, -NH-CO-CO-NH-, NH-CO-CO-NH-CH₂-, -SO₂NH-, -NHSO₂-, -SO₂NCH₃-, -NCH₃SO₂-, -NR₆-, -C(=NOH)-, or a mixture thereof; R₆ being as defined above, optionally the bivalent radical is substituted, ~~in particular by at least one C₁₋₆alkyl group;~~

X and Y, which are identical or different, represent an hydrogen or halogen atom (preferably F);

its tautomers, optical and geometrical isomers, racemates, salts, ~~hydrates~~ and mixtures thereof.

23. (Withdrawn - Currently Amended) A compound according to claim 22, wherein the Lgroup[[s]] identified in claim [[1 are]] 22 is substituted with at least one substituent, which may be selected in the group consisting of: a hydrogen atom, a halogen atom (preferably F, Cl, or Br), a hydroxyl group, a C₁₋₁₀alkyl group, an alkenyl group, an C₁₋₁₀alkanoyl group, a (C₁-C₁₀)alkoxy group, a (C₁-C₁₀)alkoxycarbonyl group, an aryl group, an aralkyl group, an arylcarbonyl group, a mono- or poly-cyclic hydrocarbon group, a -NHCO(C₁-C₆)alkyl group, -NO₂, -CN, a -Nrr' group and a trifluoro(C₁-C₆)alkyl group, in which r and r', which are identical or different, represent a hydrogen atom, a lower alkyl group, an aryl, aralkyl group, an α-aminoacid group, a sugar group or a heterocycle group, or in which r and r' taken together form a heterocyclic ring.

24. (Currently Amended) A compound according to claim 22, wherein R is -C(O)NR₇R₈ or -(CXY)C(O)NR₇R₈, ~~in particular wherein R₈ is an hydrogen atom and R₇~~

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~~is an hydroxyl group or a 2-aminophenyl group, preferably with X and Y are both halogen atoms and t is 1.~~

25. (Previously Presented) A compound according to claim 22, wherein R is an hydroxamic acid group $-(C=O)-NH-OH$, a 2,2-difluoro-N-hydroxyacetamido group $-(CF_2-(C=O)-NH-OH)$, or a N-(2-aminophenyl)acetamido group.

26. (Withdrawn - Currently Amended) A compound according to claim 22, wherein R is an electrophilic ketone, ~~in particular $(C=O)-CF_3$ or an α -ketoamides, for instance $(C=O)-(C=O)-NHMe$.~~

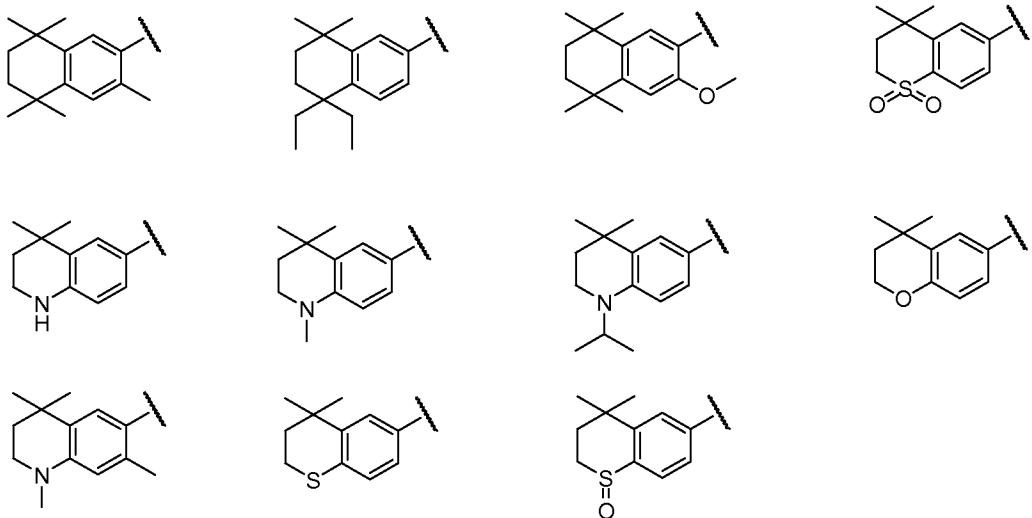
27. (Currently Amended) A compound according to claim 22, wherein R is in para or meta position of C1, ~~R is preferably in para position of C1.~~

28. (Previously Presented) A compound according to claim 22, wherein L represents -CO-NH-, -NH-CO-, -CH=CH- (cis or trans forms), -CF₂-CO-NH-, -CF₂-CO-NH-CH₂-, or -NH-CO-CO-NH-.

29. (Currently Amended) A compound according to claim 22, wherein R₃ is an hydrogen atom, OR₆, ~~in particular methoxy~~, or a C₁₋₆alkyl group, ~~in particular methyl~~.

30. (Previously Presented) A compound according to claim 22, wherein R₃ is on position 2 of the substituted naphthalene derivative.

31. (Withdrawn) A compound according to claim 22, wherein the ring carrying X₁ is selected from:



32. (Previously Presented) A compound according to claim 22, wherein the ring carrying X₂, X₃, and X₄ is selected from phenyl, pyridinyl, pyrimidinyl, isoxazolyl, thiophenyl, furanyl, pyrrolyl, pyrazolyl, imidazolyl, isothiazolyl, thiazolyl, thienyl, thienooxazolyl and triazinyl rings.

33. (Currently Amended) A compound according to claim 22, wherein the ring carrying X₂, X₃, and X₄ is phenyl, optionally substituted by a halogen atom, ~~more particularly a fluorine atom~~, a C₁₋₆alkyl group, a group of formula -OH, or OR₆.

34. (Previously Presented) A compound, which is selected from the group consisting of:

N-(4-(Hydroxycarbamoyl)phenyl)-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-carboxamide
N-(4-(2-Aminophenylcarbamoyl)phenyl)-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-carboxamide
N-(1,2,3,4-Tetrahydro-1,1,4,4-tetramethylnaphthalen-6-yl)-N'-hydroxyterephthalamide

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4-((*E*)-2-(1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalen-6-yl)vinyl)-*N*-hydroxybenzamide

4-((*Z*)-2-(1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalen-6-yl)vinyl)-*N*-hydroxybenzamide

4-(2,2-difluoro-2-(1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalen-7-yl)acetamido)-*N*-hydroxybenzamide

3-(2,2-difluoro-2-(1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalen-7-yl)acetamido)-*N*-hydroxybenzamide

4-((2,2-difluoro-2-(1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalen-7-yl)acetamido)methyl)-*N*-hydroxybenzamide

N-(4-((hydroxycarbamoyl)difluoromethyl)phenyl)-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-carboxamide

N-(4-Hydroxycarbamoyl-phenyl)-*N'*-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-oxalamide

N-(4-Hydroxycarbamoyl-benzyl)-*N'*-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-oxalamide.

35. (Previously Presented) A compound, which is selected from the group consisting of:

4-(2,2-Difluoro-2-(1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalen-7-yl)acetamido)-*N*-hydroxybenzamide

N-(1,2,3,4-Tetrahydro-1,1,4,4-tetramethylnaphthalen-6-yl)-*N*'-hydroxyterephthalamide

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4-((2,2-Difluoro-2-(1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalen-7-yl)acetamido)methyl)-*N*-hydroxybenzamide

N-(4-(Hydroxycarbamoyl)phenyl)-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-carboxamide

36. (Previously Presented) A pharmaceutical composition comprising at least one compound of formula (I), as defined in claim 22, and a pharmaceutically acceptable vehicle or support.

37. (Currently Amended) A method for the treatment of conditions mediated by HDAC, such as cancers, in particular promyelocytic leukaemia-leukaemia, or other diseases associated with abnormal cell proliferation, such as psoriasis, comprising the administration to a subject in need thereof of an effective amount of a compound as defined in claim [[22]]34.

38. (Currently Amended) A method for the treatment of central and peripheral nervous system diseases or neurodegenerative diseases associated with an excitotoxicity, such as Huntington's disease, such as polyglutamine expansion diseases, Alzheimer disease, Parkinson disease, multiple sclerosis, neuronal ischemia or amyotrophic lateral sclerosis (ALS), comprising the administration to a subject in need thereof of an effective amount of a compound as defined in claim [[22]]34.

39. (Currently Amended) A method for the treatment of fibrosis, comprising the administration to a subject in need thereof of an effective amount of a compound as defined in claim [[22]]34.

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40. (Previously Presented) A method according to claim 37, wherein the cancer is selected from promyelocytic leukaemia, prostate cancer, ovarian cancer, pancreas cancer, lung cancer, breast cancer, liver cancer, head and neck cancer, colon cancer, bladder cancer, non-Hodgkin 's lymphoma cancer and melanoma.

41. (Currently Amended) A method for reducing cancer cell proliferation, comprising the administration to a subject in need thereof of an effective amount of a compound as defined in claim [[22]]34.